



The LASRE trial: further support for laparoscopic total mesorectal excision?

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Colorectal cancer (CRC) is the third most common cancer, and second leading cause of cancer related mortality worldwide, making it a major global health burden (1). In the non-metastatic setting, the mainstay of treatment for CRC is surgery. In the surgical management of colonic cancer, laparoscopy has been shown to offer equivalent oncologic results to open surgery in various randomised clinical trials (RCTs) (2,3). In addition, laparoscopy is also associated with a quicker postoperative recovery, better cosmesis, reduced blood loss and need for analgesics (4). These additional benefits with equivalent oncologic outcomes have led to laparoscopy largely considered as the gold standard approach for colonic resection. With regard to rectal cancer however, there remains ongoing controversy regarding the role of laparoscopy and its equivalence with open total mesorectal excision (TME).

The Laparoscopy-Assisted Surgery for Carcinoma of the Low Rectum (LASRE) trial (5) was a robust, well-designed non-inferiority based RCT that compared oncologic outcomes between laparoscopic and open approaches in patients with low rectal cancer. Participating surgeons had to have performed over 100 laparoscopic TMEs, including submission of at least two videos for review. A total of 1,039 patients with low rectal cancers (median distance from dentate line 3 cm) were randomised in a 2:1 fashion to undergo laparoscopic TME or open TME. Over 60% had clinical stage II/III disease, necessitating neoadjuvant chemoradiation. Short-term secondary outcomes were

reported in this publication. From an oncologic perspective, there was no difference in rates of complete mesorectal excision (85.3% *vs.* 85.8%, $P=0.78$), negative circumferential resection margins (CRMs) (98.2% *vs.* 99.7%, $P=0.09$), distal resection margins (DRMs) (99.4% *vs.* 100%, $P=0.36$) and median lymph node yield (13 *vs.* 12, $P=0.39$).

There were however, notable non-oncologic benefits in the laparoscopic arm, in keeping with proven advantages of minimally invasive surgery. The laparoscopic group was associated with a 50 mL median reduction in blood loss (50 *vs.* 100 mL, $P<0.001$), along with significantly quicker return of flatus, bowel function, and advancement of diet. This contributed to a one-day reduction in median hospital length of stay (8.0 *vs.* 9.0 days, $P=0.008$). Additionally, laparoscopy was associated with a three-hour reduction in analgesic use (45.0 *vs.* 48.0 hours, $P=0.001$) and reduced incisional complications (2.6% *vs.* 5.1%, $P=0.04$). Conversion rates were low (2.5%), possibly as most of the cohort had low body mass index (BMI) (median BMI 23 across both groups). Laparoscopy however was associated with a significantly longer operating time (195 *vs.* 180 min, $P<0.001$).

Interestingly, anastomotic leak rates were more than twice as high in the open group (2.5% *vs.* 6.1%, $P=0.01$). Notably, there was a significantly improved sphincter preservation rate in patients undergoing laparoscopic surgery (71.7% *vs.* 65.0%, $P=0.03$). While sphincter preserving surgery is often aimed for by surgeons, one has

to wonder about the functional quality of life with such low anastomoses after neoadjuvant chemoradiation. Functional outcomes from such low anastomoses would be an equally important metric, which were unfortunately not reported.

The LASRE trial is an important addition to the literature comparing laparoscopic to open TME. In the short term, this study confirms that laparoscopy is safe when performed by experienced surgeons, and offers similar short-term oncologic outcomes to open TME, with significant benefits owing to a minimally invasive approach. Most of the cohort had low BMI (median 23.0), a factor that differs from other RCTs (6,7). Longer-term follow-up will shed light on whether this short-term equivalence is retained in the longer term. There are four previous large RCTs that have similarly compared laparoscopic to open approaches for rectal cancer. The COREAN trial (8) was a Korean RCT that included patients with stage II–III mid-to-low rectal cancer. In the short term, there was no difference in CRM positive rates or completeness of mesorectal excision. Laparoscopy was associated with less blood loss, earlier return of bowel function and less opiate use. Laparoscopy did contribute to longer operating times. Relative to 3-year oncologic outcomes, there was no difference in 3-year disease-free survival (DFS) between groups (9). At long-term follow-up; there was no difference in 10-year local recurrence, DFS or overall survival (OS) between groups (10). The COLOR II RCT (11) was a European trial that similarly compared laparoscopic and open approaches in stage I–III rectal cancer. The laparoscopic approach was associated with significantly less blood loss, quicker return of bowel function and reduced hospital stay. Laparoscopy was associated with significantly longer operating time. There was no difference in positive CRM rate, completeness of resection, overall morbidity and mortality between groups. Additionally, there was no difference in rates of ventral, parastomal hernia, bowel obstruction or genito-urinary dysfunction between groups (12,13). Oncologically, there was no difference in locoregional recurrence rates (LRRs), DFS or OS between groups (14). Together, these two prior trials demonstrated that laparoscopic rectal cancer surgery by skilled surgeons offers similar safety and oncologic outcomes to open proctectomy.

The ALaCaRT (7) and ACOSOG Z6051 (6) trials were two subsequent non-inferiority based RCTs that also compared laparoscopic to open proctectomy. In both these studies, only surgeons who were accredited after video review of procedures participated. ACOSOG Z6051 (6) was a North American study that included patients with

stage II–III rectal cancer treated with neoadjuvant therapy. There was no difference in CRM negative rates, distal margin positivity or completeness of resection between groups. The composite successful surgical dissection rates (CRM, DRM and completeness of TME) of 82% in the laparoscopic group and 87% in the open group (difference $-5.3%$, $P=0.41$) did not meet the pre-specified non-inferiority margin of 6%. Additionally, there was no difference in length of stay, re-admission within 30 days and severe complications between groups. Operative time was significantly longer with a laparoscopic approach. Conversion to open occurred in 11.3% of cases. With longer follow-up, there was no difference in 2-year DFS, loco-regional recurrence or rates of distant metastases between groups (15).

The ALaCaRT trial (7) was an Australasian RCT that reported at the same time. There was no difference in CRM, completeness of mesorectal excision and distal margin rates between groups. The successful resection rates (composite of CRM, DRM and completeness of TME) of 82% in the laparoscopic group and 89% in the open group (difference $-7.0%$, $P=0.38$) did not meet the pre specified non-inferiority margin of 8%. Longer follow-up however, did not demonstrate any difference in 2-year local recurrence, DFS or OS (16).

While early results of both trials failed to demonstrate non-inferiority of the laparoscopic approach, oncologic equivalence at longer term follow-up have since led many to accept laparoscopy as a safe alternative in rectal cancer surgery.

Including the LASRE trial, these five trials have demonstrated no difference in short term oncologic outcomes between laparoscopic and open TME. Longer term follow-up in these four trials (11,14–16) confirmed oncologic equivalence. Laparoscopy was seen almost universally to contribute to less blood loss, quicker return of bowel function, reduced analgesic requirements and shorter length of stay. *Table 1* summarizes the available outcome measures and findings of the five trials.

Based on these recent trials, there is perceived equipoise between open and laparoscopic TME. Going forward, there is increasing use of transanal TME (TaTME) and Robotic TME, particularly in the setting of mid-to-low rectal cancers, where navigation of the narrow pelvis can be increasingly challenging. With increasing adoption of the robotic platform, more centres are utilising the robotic system for pelvic surgery (17–19). Improved ergonomics, 3-D field of view, articulating instruments and the ability to

Table 1 Summary of key findings from landmark trials comparing laparoscopic to open total mesorectal excision for rectal cancer

Trial (year)	Inclusion criteria	Patient numbers	CRM positive	DRM negative	Completeness of TME	Complications	LR	DFS	Other key findings
COREAN [2010] (8,9)	Mid-to-low rectal cancer	Lap [170] vs. open [170]	2.9% vs. 4.1%, P=0.77		72.4% vs. 74.7%, P=0.41	21.2% vs. 23.5%, P=0.60	3-year: 2.6% vs. 4.9%	3-year: 79.2% vs. 72.5%	Reduced blood loss, earlier return of bowel function, reduced LOS, reduced opiate use with laparoscopy. Increased operative time with laparoscopy
COLOR II [2013] (11,14)	Cancer within 15 cm of AV	Lap [699] vs. open [345]	10% vs. 10%, P=0.85		88% vs. 92%, P=0.25	40% vs. 37%, P=0.42	3-year: 5.0% vs. 5.0%	3-year: 74.8% vs. 70.8%	Reduced blood loss, quicker return of bowel function, reduced LOS with laparoscopy. Increased operative time with laparoscopy
ACOSOG Z6051 [2015] (6,15)	Cancer within 12 cm of AV	Lap [240] vs. open [222]	12.1% vs. 7.7%, P=0.11	98.3% vs. 98.2%, P=0.91	92.1% vs. 95.1%, P=0.20	22.5% vs. 22.1%	2-year: 4.6% vs. 4.5%	2-year: 79.5% vs. 83.2%	Increased operative time with laparoscopy. No difference in LOS, severe complications
ALaCaRT [2015] (7,16)	Cancer within 15 cm of AV	Lap [238] vs. open [237]	7% vs. 3%, P=0.06	99% vs. 99%, P=0.67	87% vs. 92%, P=0.06	18.5% vs. 26.4%	2-year: 5.4% vs. 3.1%	2-year: 80% vs. 82%	Reduced blood loss, earlier return of bowel function with laparoscopy. Increased operative time with laparoscopy. No difference in LOS, complications or analgesic requirements
LASRE [2022] (5)	Low rectal cancer	Lap [712] vs. open [358]	1.8% vs. 0.3%, P=0.09	99.4% vs. 100%, P=0.36	85.3% vs. 85.8%, P=0.78	13.0% vs. 17.2%, P=0.07	NR	NR	Reduced blood loss, increased sphincter preservation, quicker return of bowel function with laparoscopy. Longer operative time with laparoscopy

AV, anal verge; Lap, laparoscopic; CRM, circumferential resection margin; DRM, distal resection margin; TME, total mesorectal excision; LR, local recurrence; NR, not yet reported; DFS, disease-free survival; LOS, length of stay.

operate in narrow spaces are some of the potential benefits with robotic surgery. Cost however, remains a prohibitive factor for wider adoption of the robotic platform.

The ROLARR trial (20) was the first RCT comparing a robotic approach to laparoscopy in rectal cancer. This trial showed no difference in conversion rates, which was its primary outcome. In addition, it reported no difference in CRM positive rates, genitourinary dysfunction or complication rates between groups. This trial included rectosigmoid and upper rectal cancers, rather than limiting inclusion to mid-to-low rectal cancers only, which is where most of the technical challenges of operating in a narrow pelvis arise. The REAL trial (18) was a multicentre RCT from China that compared robotic and laparoscopic approaches to mid and low rectal cancers (<10 cm from the anal verge). There was a significant reduction in CRM positivity in the robotic group (4.0% vs. 7.2%, P=0.023).

Additionally, patients in the robotic group had fewer postoperative complications, with lesser intra-operative blood loss, quicker recovery and reduced length of stay. Robotic surgery was associated with a significant increase in sphincter preservation (22.7% vs. 16.9%). This was the first study to demonstrate short-term oncologic superiority of the robotic platform to laparoscopy. Long-term follow-up will help clarify if short-term oncologic superiority translates to long-term survival differences.

With TaTME also gaining in popularity, the COLOR III trial (21) is a current multicentre RCT that is evaluating for oncologic difference in TME in patients with mid-to-low rectal cancers. The TaLAR trial (22) is a similar RCT that is also comparing surgical quality and oncologic outcomes between laparoscopic and TaTME.

The debate around the optimal approach to rectal cancer is evolving into a four-way conversation involving open,

laparoscopic, robotic and TaTME approaches. There is accepted equipoise between laparoscopic and open approaches to rectal cancer. The LASRE trial is a further high quality RCT that re-affirms the safety and feasibility of laparoscopic TME when performed by experienced surgeons. Early studies have shown robotic and TaTME approaches to be safe and comparable to laparoscopy, with longer-term results awaited. For now, as with many complex scenarios in colorectal oncology, selection of the optimal operative approach for a patient with rectal cancer would be based on the individual patient, surgeon expertise and institutional resources.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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